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APPLICANT(S):	**H. Garrett WADA et al.**
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Total Number of Pages in This Submission	14

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Filing Date	7/2/2003
First Named Inventor	H. Garrett WADA et al.
Art Unit	1641
Examiner Name	Deborah A. DAVIS
Attorney Docket Number	100/07211

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
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- ☐ Drawing(s)
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Firm Name	CALIPER LIFE SCIENCES, INC.		
Signature	Ann C. Petersen		
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. No.	:	10/613,220	Confirmation No.:	7051
Applicants	:	H. Garrett Wada et al.		
Filed	:	07/02/2003		
TC/A.U.	:	1641		
Examiner	:	Deborah A. Davis		
Docket No.	:	100/07211		
Customer No.	:	021569		
Title	:	Microfluidic Analytic Detection Assays, Devices, and Integrated Systems		

Commissioner for Patents
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Response to Notification of Non-Compliant Appeal Brief

Sir:

In response to the Notification of Non-Compliant Appeal Brief mailed on January 31, 2007, Applicants are herewith submitting an amended Appeal Brief that contains the headings "Evidence Appendix" and "Related Proceedings Appendix" with statements that these sections are not applicable to the present appeal. Except for the added appendix headings and statements, the amended Appeal Brief submitted herewith is identical to the Appeal Brief submitted by Applicants on August 22, 2006, under 37 CFR §1.192 in response to the Examiner's Final Action mailed March 23, 2006.

Applicants do not believe that any fees are due, but please charge Deposit Account No. 03-0177 if there are any fees associated with this communication or during the pendency of this application.

I. REAL PARTY IN INTEREST:

The real party in interest is Caliper Life Sciences, Inc. (formerly Caliper Technologies Corp.), which is the assignee of the entire right, title, and interest in the application involved in the appeal. The present application is a divisional of U.S. Patent Application No. 09/641,468, filed August 17, 2000, now U.S. Patent No. 6,613,581, which claims the benefit of and priority to U.S. Provisional Patent Application No. 60/150,923, filed August 26, 1999. Assignment of the parent application by the inventors, H. Garrett Wada and Matthew B. Murphy, to Caliper Technologies Corp. is recorded on Reel/Frame 010518/0248 in the Assignment Division of the United States Patent and Trademark Office. A request for assignment of the present application from Caliper Technologies Corp. to Caliper Life Sciences, Inc. has been filed with the Assignment Division of the United States Patent and Trademark Office.

II. RELATED APPEALS AND INTERFERENCES:

The application of interest in the pending appeal is U.S. Application Serial No. 10/613,220, which was filed on July 02, 2003. The application of interest claims priority from U.S. Patent Application No. 09/641,468, filed August 17, 2000, now U.S. Patent No. 6,613,581, which claims the benefit of and priority to U.S. Provisional Patent Application No. 60/150,923, filed August 26, 1999. Appellants and the Appellants' legal representative are not aware of any appeals or interferences that would directly affect or be directly affected by, or have a bearing on, the Board's decision in the pending appeal.

III. STATUS OF CLAIMS:

Claims 1–23 are pending in the application. Claims 1–23 have been rejected. The rejection of each of claims 1–23 is at issue in this appeal.

IV. STATUS OF AMENDMENTS:

No amendments have been filed subsequent to the final rejection.

V. SUMMARY OF CLAIMED SUBJECT MATTER:

Claim 1, which recites a system for detecting a component of interest in a sample, is the sole independent claim currently on appeal. The claimed system is herein described primarily with reference to Figure 1 and the text describing Figure 1 in paragraph 0050, which begins at the bottom of page 11 of the application. In addition, paragraphs 0022, 0044, 0045, 0083, and 0112 on pages 5, 10, 10, 20, and 28, respectively, paragraphs 0118–0121, beginning on page 29, and paragraphs 0122–0131, beginning on page 30, are referenced. The following explanation is intended to be illustrative rather than limiting.

The system comprises a microfluidic device, a fluid direction system fluidly coupled to the microfluidic device, a control system operably linked to the fluid direction system, and a detection system. The microfluidic device comprises first **104** and second **110** microscale channels. Second microscale channel **110** is fluidly coupled to first microscale channel **104** and is downstream from first microscale channel **104**. That second microscale channel **110** is downstream from first microscale channel **104** is supported in paragraph 0050, beginning on page 11, which states that a sample is introduced from sample well **102** into channel **104** and is directed into channel **110** after leaving channel **104**. As defined in paragraph 0045 on page 10, "The term 'downstream' refers to a location in a channel or microfluidic device that is farther along the channel or plurality of channels in a selected direction of fluid or material flow, relative to a selected site or region."

The first microscale channel includes a gel filled component separation region, as described in lines 4–6 of paragraph 0044 on page 10 and paragraph 0083 on page 20. A first detection region **106** is positioned within first microscale channel **104**. The second microscale channel is configured to contain a particle set, which in the embodiment illustrated in Figure 1 is released from particle well **112**. A second detection region **114** is positioned within second microchannel **110**. Second detection region **114** includes a particle stacking region, as described in lines 6–10 of paragraph 0050 on page 12. The aforementioned detection system is configured to be positioned proximal to the first and second detection regions. Detection systems are discussed in paragraphs 0122–0131, beginning on page 30.

The microfluidic device also comprises a binding region fluidly coupled to or within the first microscale channel. A source of a component-binding moiety that is capable of

binding to the component of interest is fluidly coupled to the binding region. As described in paragraph 0022 on page 5, the component-binding moiety may be flowed concurrently with the sample through first microscale channel **104**, resulting in a binding region within the first microscale channel. Alternatively, as described in paragraph 0112 on page 28, the component-binding moiety may be added to separated components as they elute from the separation matrix, for example being added within elution region **108**, thereby resulting in a binding region fluidly coupled to the first microscale channel.

The fluid direction system fluidly coupled to the microfluidic device is configured to transport a sample through at least the first and second microscale channels. The control system operably linked to the fluid direction system is configured to instruct the fluid direction system to deliver or transport the sample through at least the first and second microscale channels. Fluid direction and control systems are described in paragraphs 0118–0121, which begin on page 29.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL:

Applicants respectfully request that the following grounds of rejection be reviewed on appeal:

Claims 1–23 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Nelson et al. US 6,007,690 ("Nelson") in view of Spence et al. US 6,540,895 ("Spence").

VII. ARGUMENT:

Claims 1–23 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Nelson in view of Spence. "The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness." *See* MPEP § 2142. To establish a *prima facie* case of obviousness, three basic criteria must be met: the prior art references must teach or suggest all the claim limitations; there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art,

to modify the reference or to combine reference teachings; and there must be a reasonable expectation of success. *See* MPEP § 2143.

The prior art references neither teach nor suggest all the claim limitations of Applicants' independent claim 1. At a minimum, neither Nelson nor Spence teaches a second microscale channel configured to contain a particle set that is downstream from a first microscale channel comprising a gel filled component separation region. In addition, neither Nelson nor Spence teaches detection regions associated with both a first and a second microscale channel such as are recited in Applicants' claim 1.

One of many described uses for Applicants' claimed system is performing western blots, also referred to as western analysis. *See* paragraph 0006 on page 2. Western blotting or analysis is described in paragraph 0003, which begins on page 1 of the application. The standard procedure involves first fractionating a protein mixture, generally by denaturing gel electrophoresis, and then transferring and immobilizing the mixture onto a solid membrane of either microcellulose or nylon by electroblotting. This standard procedure is time consuming and labor intensive. When a western analysis type procedure is performed on Applicants' high throughput microscale system, a protein mixture is fractionated in the first microscale channel (e.g., channel **104** in Figure 1) and immobilized in the particle stacking region within the second microscale channel (e.g., region **114** in channel **110**). Thus, having the second microscale channel and its particle stacking region ***downstream*** from the first microscale channel and its component separation region is fundamental to this embodiment of Applicants' invention.

The Examiner has alleged that Applicants' first microscale channel corresponds to Nelson's main electrophoretic flowpath and that Applicants' second microscale channel corresponds to Nelson's enrichment channel. Fundamental to the invention of Nelson is that the enrichment channel be ***upstream*** from the main electrophoretic flowpath. As stated in column 2, lines 51–53 (emphasis added), "The enrichment channel serves to enrich a particular fraction of a liquid sample for ***subsequent*** movement through the main electrophoretic flowpath." No purpose would be served in the invention of Nelson by having sample enrichment take place ***after*** (i.e., downstream from) the electrophoretic separation channel.

Specifically, on page 2 of the non-final Office action mailed October 6, 2005, the Examiner interpreted electrophoretic flowpath **236** of Figure 18 of Nelson as a gel separation region. Therefore, by the Examiner's interpretation, the first microscale channel of Applicants'

claim 1 would correspond to channel **236** of Nelson. The Examiner then stated on page 3 of the Office action, "the enrichment channel can employ paramagnetic beads that are coated with affinity medium and can be retained in the channel...." Thus, the Examiner has interpreted Applicants' second microscale channel as corresponding to the enrichment channel of Nelson. The enrichment channel illustrated in Figure 18, as well as in Figures 15–17, is identified as channel **230**. As can be seen in Figures 15–18, channel **230** is ***upstream*** from channel **236**.

In the final Office action mailed March 23, 2006, the Examiner states, "the enrichment zone taught in the reference of Nelson, which the examiner interprets as applicant's particle-stacking region can be alternatively configured to be positioned in the first ***and*** the second channels (see Figure 19, #280). Therefore, the second microscale channel containing the particle set would be downstream from the first microscale channel that is fluidly coupled to the first channel...." The Examiner has not identified the channels in Figure 19 that are alleged to correspond to Applicants' first and second channels, and the quoted passage is somewhat unclear. However, as is clear from examining Figure 19 and reading the explanatory text in column 18, lines 33–56, all of the enrichment channels **280** are ***upstream*** from the electrophoretic flowpaths **284** to which they are fluidly coupled. Further, none of the enrichment channels **280** illustrated in Figure 19 can be considered to be downstream from any of the electrophoretic flowpaths **284** illustrated in Figure 19. Applicants must respectfully disagree with the Examiner's reasoning if, for example, enrichment channel **280** in the bottom line of Figure 19 is being considered by the Examiner to be downstream of electrophoretic flowpath **284** in the top line of Figure 19. Elements in different lines of Figure 19 do not share a common flowpath and so cannot be considered to be either upstream or downstream of one another. The only apparently shared flowpath is illustrated in Figure 19 at **281**, and this element is identified in the text (column 18, line 35, emphasis added) as a "***branched*** sample supply manifold."

As described by the Examiner on page 4 of the non-final Office action mailed October 6, 2005, the Spence reference "teaches cell sorting utilizing microfluidic system controlled by a computer or microprocessor that control fluid flow." Spence was cited in the Office action as teaching a control system, which the Examiner acknowledged was absent from the teachings of Nelson. Spence is not alleged to teach, nor does the reference teach, a second microscale channel configured to contain a particle set that is downstream from a first microscale

channel comprising a gel filled component separation region. Therefore, Spence cannot supply the limitation missing from Nelson.

As previously noted, both Nelson and Spence are silent with regard to detection regions associated with both first and second microscale channels such as are recited in Applicants' claim 1. Nelson teaches detection regions illustrated in Figure 18 at **278** and in Figure 19 at **286**. These detection regions are associated with electrophoretic flowpaths. No detection regions are associated with the enrichment channels in these or any other figures, nor are any such second detection regions described in the text. Spence does not teach either a first microscale channel comprising a gel filled component separation region or a second microscale channel configured to contain a particle set. Therefore, Spence cannot teach detection regions associated with such channels.

As demonstrated above, the combination of Nelson and Spence neither teaches nor suggests all of the claim limitations of Applicants' independent claim 1. Therefore, the Examiner has not met the initial burden of factually supporting a *prima facie* conclusion of obviousness. As a result, claim 1 is nonobvious. Claims 2–23 depend directly or indirectly from independent claim 1. Any claim depending from a nonobvious claim is also nonobvious. *See* MPEP § 2143.03 and *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Therefore, dependent claims 2–23 are also allowable over the combined references.

Applicants wish to point out that the Examiner alleged in the final Office action mailed March 23, 2006, that the information disclosure statement filed October 14, 2003, fails to comply with 37 CFR § 1.98(a)(2), which requires legible copies of cited foreign patent documents and non-patent literature publications. The Examiner did not raise this issue in any of the three previous Office actions. Had the Examiner raised this issue earlier, Applicants would have had the opportunity to state that all of the required documents accompanied the information disclosure statement filed with the parent application. Under 37 CFR § 1.98(d), the references need not be sent a second time if the references were "previously submitted to, or cited by, the Office in an earlier application" *and* the "earlier application is properly identified in the information disclosure statement and is relied on for an earlier effective filing date" *and* "the information disclosure statement submitted in the earlier application complies with paragraphs (a) through (c) of this section." All of these conditions were met.

VIII. CONCLUSION:

Thus, for the foregoing reasons, Appellants maintain that their claims are allowable over the combined references and respectfully request that the present rejections of the claims under 35 U.S.C. § 103(a) be withdrawn.

Respectfully submitted,

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IX. APPENDIX OF CLAIMS ON APPEAL:

1. A system for detecting a component of interest in a sample, the system comprising:

(i) a microfluidic device comprising:

(a) a first microscale channel comprising a gel filled component separation region;

(b) a second microscale channel downstream from the first channel that is fluidly coupled to the first channel, the second channel configured to contain a particle set therein;

(c) a binding region fluidly coupled to or within the first channel;

(d) a source of a component-binding moiety fluidly coupled to the binding region which is capable of binding to the component of interest;

(e) a first detection region within the first channel; and

(f) a second detection region within the second channel which includes a particle stacking region within the second detection region;

(ii) a fluid direction system fluidly coupled to the microfluidic device, which fluid direction system is configured to transport the sample through at least the first and second microscale channels;

(iii) a control system operably linked to the fluid direction system, which control system is configured to instruct the fluid direction system to deliver or transport the sample through at least the first and second microscale channels; and

(iv) a detection system which is configured to be positioned proximal to the first and second detection regions.

2. The system of claim 1, wherein the control system comprises a computer and software, which software analyzes signals produced from detection at the first and second detection regions.

3. The system of claim 2, wherein the computer includes software which is programmed to direct fluid movement in the system.

4. The system of claim 3, wherein the software directs one or more of:

movement of the sample through the component separation region of the first channel, resulting in separated components;

movement of a particle set and the separated components to the binding region, resulting in binding of the separated components to the particle set;

movement of the component-binding moiety to the binding region, resulting in binding of the component-binding moiety to the component of interest; and,

movement of the particle set, separated components, and the component-binding moiety to the particle stacking region in the second detection region, where the component-binding moiety is detected, thereby detecting the component of interest.

5. The system of claim 4, wherein the software further directs movement of one or more of a buffer solution and a blocking solution through the binding region.

6. The system of claim 4, wherein the software directs movement of the particle set from a source of the particle set to the particle stacking region.

7. The system of claim 4, wherein the software directs a washing solution to flow through the binding region.

8. The system of claim 1, wherein the component of interest is a protein and the component binding moiety is a protein-binding moiety.

9. The system of claim 1, wherein the component-binding moiety is an antibody.

10. The system of claim 1, wherein the component of interest is a carbohydrate and the component binding moiety is a carbohydrate-binding moiety.

11. The system of claim 10, wherein the carbohydrate-binding moiety is a lectin specific to the carbohydrate.

12. The system of claim 1, wherein the component-binding moiety is a lectin.

13. The system of claim 1, wherein the component-binding moiety is avidin or biotin.

14. The system of claim 1, wherein the component of interest comprises avidin and the component-binding moiety is biotin.

15. The system of claim 1, wherein the component of interest comprises biotin and the component-binding moiety is avidin.

16. The system of claim 1, wherein the fluid direction system is an electrokinetic based fluid direction system.

17. The system of claim 1, wherein the fluid direction system is a pressure based fluid direction system.

18. The system of claim 1, wherein the component separation region is a polyacrylamide gel filled region.

19. The system of claim 1, further comprising a source of a particle set fluidly coupled to the second microscale channel, the particle set comprising particles made from a polymeric material, a silica material, a ceramic material, a glass material, a magnetic material, a metallic material, or an organic material.

20. The system of claim 1, further comprising a source of a particle set fluidly coupled to the second microscale channel, the particle set comprising particles made from PVDF, polyamide, nylon, or nitrocellulose.

21. The system of claim 1, wherein the particle stacking region comprises a barrier on which a particle set may be fixed.

22. The system of claim 1, wherein the detection system comprises a chemiluminescent, fluorescent, or colorimetric detector.

23. The system of claim 1, wherein the binding region is located within a third channel that intersects and fluidly connects the first and second channels.

X. EVIDENCE APPENDIX:

None.

XI. RELATED PROCEEDINGS APPENDIX:

None.